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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,827	01/15/2004	Michael R. Rosen	13533/48003	5518

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
02/15/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,827	ROSEN ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments and declaration filed on December 2, 2010 010 have been received and entered. Claims 20, 49, 51, 57, 59, 65-70 and 71 are pending in this application.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group was found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 57, 59, 65-70 and 71 are under consideration in the instant application.

Oath/Declaration

The Rosen declaration on December 2, 2010, 2007 filed under 37 CFR 1.132 is sufficient to overcome the rejection of 20, 49, 51, 57, 59, 65-70 and 71 based upon reference of Rosen et al (US patent application no 20020187948, dated 12/12/2002, 06/06/2001, IDS) or Rosen et al (WO 02/098286 , dated 12/12/2002, IDS), applied under 103(a) rejection.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 20, 49, 51, 57, 59, 65-70 and 71 were rejected under 35 U.S.C. 103(a) as being unpatentable over Rosen et al (US patent application no 20020187948, dated 12/12/2002, 06/06/2001, IDS) or Rosen et al (WO 02/098286 , dated 12/12/2001, IDS), Lee et al (Molecular Therapy, 2001, 857–866, IDS) and Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, IDS). The rejection is withdrawn in view of is withdrawn in view of declaration by the applicant indicating that cited primary art of Rosen et al is not by others.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 49, 51, 57, 59, 65-70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feld et al (US patent no 7294333, dated 11/13/2007, filed on 10/20/2000), Lee et al (Molecular Therapy, 2001, 857-866, IDS, hereafter Lee 1), Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002, art of record, hereafter Lee 2), and Qu et al (Circulation res. 2001, 89:e8-14, IDS).

It is noted that method claims require one active method step comprising introducing the composition of the invention comprising genetically modified mesenchymal stem cell (MSC) to the heart or contacting human cardio myocyte with the composition of the invention.

With respect to claim 20, and 65, Feld et al teach allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel. Regarding claims 49, 51, 57, 59 and 66, Feld et al teach a method of modifying the electrophysiological function of a heart of an individual and treating atrial fibrillation or ventricular tachycardia, the method comprising: (a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel; thereby modifying the electrophysiological function of the heart and treating atrial fibrillation or ventricular tachycardia. It is further disclosed that each implanted cell of said allogeneic or autogeneic fibroblasts forms said functional ion channel following induction, wherein inward-rectifier potassium ion channel is Kir2.1 (see claims 1-3 of '333). It is further disclosed that cells are implanted in the heart by injection (see col. 17, line 14). Feld et al contemplated other cell types can be utilized to accomplish the cells posses functional gap junctions and functional ion channels including fibroblasts, skeletal myoblasts that are autologous, allogenic, or xenogenic origin (see col. 14, lines 32-36). Feld et al further disclose that the cells transplanted generate specific structural and function interactions with the cardiomyocytes via the gap junction which can be either inherent to the transplanted cells or the product of over expressed exogenes (see col. 14, lines 36-40). Regarding claims 70-71, it is disclosed that the nucleic acid construct includes at least one promoter sequence for driving the transcription of the first and second polynucleotide regions (see col. 4, lines 45-57). While Feld et al teach a composition and method comprising a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel

polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel, but differ from claimed invention by not disclosing cells and ion channel being MSC and HCN2 respectively.

Lee et al (1) provide motivation to use MSC as gene delivery vehicle for treating various conditions. Lee et al teach an ex vivo culture and expansion capabilities and multi potential nature of hMSCs to make hMSCs an attractive cellular vehicle for gene delivery applications. Lee et al show genetically transduced MSCs expanded in culture and maintain the stem cell phenotype and stable transgene expression for over 6 months (see page 858, col. 1, para. 1), but differ from claimed invention by not disclosing injecting MSC to heart or cardiac cell.

Lee et al (2) teach a composition comprising a recombinant mammalian cell that is genetically engineered to express connexin 43(Cx43) protein intended for establishing electrical coupling between cardiomyocytes and recombinant mammalian cells, wherein the mammalian cells are mesenchymal stem cells. It is reported that the cell may be autologous or allogeneic to the host including human that requires transplantation of genetically modified cell (see col. 14, lines 47-55). Lee et al also teach that Cells may be autologous, allogeneic, or xenogeneic with respect to the host. Thus, teaching of Lee embraces using genetically modified human mesenchymal stem cell to treat a host that is human (see col. 14, lines 56-60, col. 5, line 21, col. 10, line 8).

Regarding claims 49, 57, 59, 66 and 67, Lee et a teach a method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells which have been genetically engineered to express a connexin 43 (Cx43) protein, wherein the mammalian cells are mesenchymal stem cells (e.g. claims 1 and 2). It is noted that Lee et al teach that “electrical coupling" means the interaction between cells which allows for intracellular communication between cells so as to provide for electrical conduction between the cells in which electrical excitation of cells through gap junction in the muscle leads to muscle contraction (see col. 10, 20-25). Thus, method of electrical coupling for inducing current is accomplished by injecting MSC to cardiomyocyte in the heart to express the transgene so as to provide for electrical conduction through formation of gap junction meeting the limitation of claims. Regarding claim 51, Lee et al teach a method for treating a cardiac conduction disturbance in a host, the method comprising: introducing into cardiac tissue of said host a therapeutically effective amount of a recombinant mammalian cell genetically modified to express a connexin 43 proteins; wherein the recombinant mammalian cell is a mesenchymal stem cell, and wherein the cell is autologous or allogeneic to the host, wherein said introducing is performed by injection into cardiac tissue of the host, or is performed by cardiovascular infusion into the host, and wherein said introducing is effective to establish an electrical connection between the recombinant cell and a myocardial cell of the host cardiac tissue; and wherein the cardiac conduction disturbance in the host is treated (see claim 8). It is noted that in a preferred embodiment Lee et al report that the host is a human. Further, Lee teaches the methods may also be utilized in combination with other cardiac therapies when appropriate. While Feld, Lee (1) and Lee et al (2) teach all the limitation of the pending claims, but differed from claimed invention by not disclosing MSC comprising nucleic acid encoding HCN2.

The deficiency of Lee is cured by Qu who reported an adenoviral construct comprising nucleic acid encoding HCN2. Qu et al teach treatment of both genetically modified adult and neonatal cells with the AdHCN2 construct resulted in expression of high current levels, with faster activation in neonate (Figures 1B and 1C) (see page 2, col. 2, para. 3). Qu et al suggest that the obvious implications for future efforts would be to alter cardiac rhythm through the regional over expression of selective HCN isoforms. It is suggested that rate can be enhanced by increasing current level, if the expressed current activates at a physiologically relevant threshold voltage in the target tissue (see page 6 (e13), col. 1, para. 3).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition and method disclosed by Feld by substituting the ion channel with one disclosed by Qu. One of ordinary skill in the art would be motivated to use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current to alter cardiac rhythm through the regional over expression of HCN isoforms (supra). Furthermore, one of ordinary skill in the art would be further motivated to substitute the fibroblast cells with MSC to deliver transgene to the heart, with reasonable expectation of successfully forming gap junction with cardiac cells. One of ordinary skill in the art would reasonably conclude that the composition comprising MSCs form gap junction when directly administered to the heart of a subject particularly since Lee taught hMSCs engrafts in the myocardium with recipient MCS (supra). Therefore, given that MSC including human MSC were available for use to express gene of interest as per the teachings of Lee (1 and II), it would have obvious for one of ordinary skill in the art to use genetically modified MSC as a gene delivery vehicle in the method of Feld. One of skill in the art would have had a reasonable expectation of success in combining the teachings because Lee et al (2) had already disclosed establishing electrical coupling between cardiomyocytes and genetically modified mesenchymal stem cells, while Qu provided relevant information about a construct comprising HCN2 for inducing pacemaker current in the heart cells to alter cardiac rhythm. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Response to arguments

Applicants' disagree with the rejection and argue that the applicants were the first to discover that undifferentiated MSC are able to form functional low resistance junction with cardiomyocyte as evident from the specification (see figure 3A) and post filing art of Valianus et al (Journal of Physiology, 2004, 617). Applicant assert that Feld et al describe only the differentiated fibroblast from the NIT3T3 cells that are transfected with ion channel as use of undifferentiated cells would cause tumor. Regarding Lee (1) and Lee (2) , applicant argues that Lee list MSC as useful recombinant mammalian cell for implantation but provides no data

regarding their use (see page 7 and 8 of the arguments). Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that applicants' argument that combination of reference failed to recognize MSC form gap junction is not persuasive. MPEP2144 (IV) states "[I]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed.Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). To the extent, Lee (1) and Lee (2) provide explicit motivation to use recombinant MSC as gene delivery vehicle for treating various conditions including by transgene expression for over 6 month, the rejection is applicable to the instant case. Additionally, contrary to applicants' that arguments that instant application is for the first time discovered that undifferentiated mesenchymal stem cell (MSC) are able to form gap junction with cardiomyocyte, it should be noted that such was known in prior art that was previously made of record (see figure 6 and abstract of Wang et al, office action 09/2/2010, reference not relied for the instant rejection), Applicant do not rebut the reference of Lee (1) thus appears to agree with the examiner's position that the reference provide motivation to use MSC as gene delivery vehicle. Therefore, to the extent, Lee (1) and Lee (2) provide explicit motivation to use recombinant MSC as gene delivery vehicle for treating various conditions including cardiac condition, one of ordinary skill in the art would conclude that any resulting effect including formation of gap junction would be implicit to the delivery of a recombinant MSC to the heart.

In response to applicant's argument that Lee (2) lists mesenchymal stem cell as useful recombinant cell for implantation but provide no data regarding their use, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of

the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). It should be noted that claims 51, 57,59, 66 and 67 are broad and recite only one active method step of (i) introducing directly into the human's heart the composition of the invention in an amount sufficient to induce pacemaker current. In this regard, Feld et al teach a method comprising: (a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual by injection, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel; thereby modifying the electrophysiological function of the heart (supra). Specifically, Feld et al disclose a nucleic acid construct comprising: (a) a first nucleic acid construct including a first polynucleotide region encoding at least one first polypeptide capable of forming a functional ion channel or transporter when expressed within a cell; and (b) a second nucleic acid construct including a second polynucleotide region encoding at least one second polypeptide capable of forming a functional gap junction when expressed within the cell that includes connexin 43 (see col. 4, lines 50-55). Thus, Feld et al clearly teach the claimed active method step, but differ from claimed invention by not explicitly disclosing use of genetically modified MSC as vehicle to deliver transgene and ion channel being HCN2. Lee et al (1) and Lee (2) are applied to the extent they cure the deficiency of Feld by providing motivation to use recombinant MSC as gene delivery vehicle for treating various conditions and implanting genetically modified MSC to the heart.

With respect to applicants' argument that there is no teaching or suggestion in Lee to transfect the cells with a different nucleic acid, it should be noted that such is taught by Feld. To the extent that Feld describes a composition comprising recombinant MSC capable of expressing ion channel and capable of forming gap junction, the rejection is applicable to the instant case (emphasis added). Qu et al teach HCN ion channel, preferably HCN2 could be expressed in mammalian cells in order to induce pacemaker current in heart. There is no requirement for Qu et al. to teach that which is clearly taught by Feld and Lee et al. It should be noted that prior art recognized that hMSC forms electrical coupling with cardiomyocytes and gene could be delivered to the heart cells or cardiomyocyte, while HCN2 over expression induces pacemaker

current in mammalian heart. A person of skill in the art would be motivated to express HCN2 in the recombinant MSC disclosed by Lee thereby inducing the pacemaker current in the cardiac tissue in the treatment of cardiac rhythm disorder, with a reasonable expectation of success. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Primary Examiner, Art Unit 1632